

NDA 21-105
Page 3

Rx only

Sulfamethoxazole and Trimethoprim Tablets, USP and Phenazopyridine Hydrochloride Tablets, USP

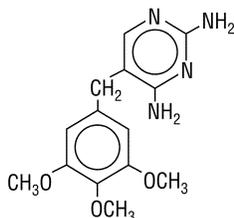
THE PRODUCTS ARE INTENDED ONLY FOR USE AS DESCRIBED. For use of the individual components when dispensed as medications outside this combination package for treating urinary tract infections (UTI), please see the package inserts for the individual products.

DESCRIPTION

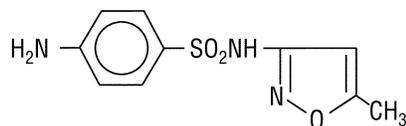
This product consists of trimethoprim/sulfamethoxazole double strength (160 mg/800 mg) tablets and phenazopyridine hydrochloride 200 mg tablets for oral administration.

Trimethoprim/sulfamethoxazole double strength tablets. Trimethoprim/sulfamethoxazole double strength is a synthetic antibacterial combination product. Each trimethoprim/sulfamethoxazole double strength tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Trimethoprim is 2,4-pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl)methyl]. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.32, the molecular formula $C_{14}H_{18}N_4O_3$, and the following structural formula:



Sulfamethoxazole is benzenesulfonamide, 4-amino-N-(5-methyl-3-isoxazolyl). It is an almost white, odorless, tasteless compound with a molecular weight of 253.28, the molecular formula $C_{10}H_{11}N_3O_3S$, and the following structural formula:

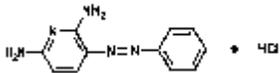


Inactive Ingredients: Each trimethoprim/sulfamethoxazole double strength tablet contains magnesium stearate, pregelatinized starch and sodium starch glycolate.

Phenazopyridine Hydrochloride tablets. Each round maroon tablet contains 200 mg phenazopyridine hydrochloride, USP for oral administration. Phenazopyridine Hydrochloride is chemically designated 2,6-pyridinediamine, 3-(phenylazo) monohydrochloride with a molecular weight of 249.70, the molecular formula $C_{11}H_{11}N_5 \cdot HCl$, and the following structural formula:

NDA 21-105

Page 4



Inactive Ingredients: Each phenazopyridine hydrochloride tablet contains acacia, carnauba wax, confectioner's sugar, corn starch powder, edible white ink, gelatin, hydrogenated vegetable oil, lactose, magnesium stearate, Opalux AS-3942 dark maroon, sodium starch glycolate, sucrose, talc powder and white bee's wax.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Trimethoprim/Sulfamethoxazole: Trimethoprim/sulfamethoxazole is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound, and metabolized forms; sulfamethoxazole also exists as the conjugated form. The metabolism of the sulfamethoxazole occurs predominately by N₄-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives. The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms. Approximately 44% of trimethoprim and 70% sulfamethoxazole are bound to plasma proteins. The presence of 10% of sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Peak blood concentrations for individual components (trimethoprim and sulfamethoxazole) occur 1 to 4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8 to 10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment (see **DOSAGE AND ADMINISTRATION** section). Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. During administration of 160 mg of trimethoprim and 800 mg of sulfamethoxazole bid, the mean steady-state plasma concentration of trimethoprim was 1.72 µg/mL. The steady-state mean plasma concentrations of free and total sulfamethoxazole were 57.4 µg/mL and 68.0 µg/mL, respectively. These steady-state concentrations were achieved after three days of administration.

Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N₄-acetylated metabolite. When administered together, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both trimethoprim and sulfamethoxazole distribute to sputum, vaginal fluid and middle ear fluid; trimethoprim also distributes to bronchial secretion, and both pass the placental barrier and are excreted in breast milk.

NDA 21-105

Page 5

Phenazopyridine Hydrochloride: Following oral administration, phenazopyridine is excreted by the kidneys, with as much as 65% of an oral dose being excreted unchanged in the urine.

Trimethoprim/Sulfamethoxazole and Phenazopyridine Hydrochloride: In a prospective two-way crossover drug interaction study between trimethoprim/sulfamethoxazole double strength and phenazopyridine hydrochloride (200 mg) administered first singly for 3 days, then in combination for an additional 3 days to 12 healthy female subjects, it was determined that the coadministration of the two drug products resulted in significantly greater plasma concentrations of trimethoprim, sulfamethoxazole, or phenazopyridine compared to when either drug was administered alone. The median increase in plasma concentrations was 29% for trimethoprim (range: -18% to 132%), 17% for sulfamethoxazole (range: -36% to 110%), and 60% for phenazopyridine (range: -79% to 474%), compared to when either trimethoprim/sulfamethoxazole or phenazopyridine was administered alone. The median (range) plasma concentrations of trimethoprim, sulfamethoxazole, and phenazopyridine at the end of combination treatment were 4.0 (2.3 - 6.9) µg/mL, 100.0 (56.4 - 185) µg/mL, and 26.5 (5.9 - 263) ng/mL, respectively.

Microbiology

Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with *para*-aminobenzoic acid (PABA). Thus, trimethoprim/sulfamethoxazole blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with both trimethoprim and sulfamethoxazole in combination than with either trimethoprim or sulfamethoxazole alone.

Trimethoprim and sulfamethoxazole have been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-negative microorganisms

Escherichia coli
Klebsiella species
Enterobacter species
Morganella morganii
Proteus mirabilis
Proteus vulgaris

Susceptibility Testing Methods

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs

NDA 21-105

Page 6

should be determined using a standardized procedure. Standardized procedures are based on a dilution method^{1,2} (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trimethoprim/sulfamethoxazole powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤2/38	Susceptible (S)
≥4/76	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trimethoprim/sulfamethoxazole powder should provide the following range of values:

<u>Microorganism</u>		<u>MIC (µg/mL)</u>
<i>Escherichia coli</i>	ATCC 25922	≤0.5/9.5
<i>Haemophilus influenzae</i> ^a	ATCC 49247	0.03/0.59 – 0.25/4.75
<i>Streptococcus pneumoniae</i> ^b	ATCC 49619	0.12/2.4 – 1/19

^a This quality control range is applicable only to *Haemophilus influenzae* ATCC 49247 tested by broth microdilution procedure using *Haemophilus* Test Medium (HTM)^{1,2}.

^b This quality control range is applicable to tests performed by the broth microdilution method only using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood^{1,2}.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure^{5,6} requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 1.25/23.75 µg of trimethoprim/sulfamethoxazole to test the susceptibility of microorganisms to trimethoprim/sulfamethoxazole.

NDA 21-105

Page 7

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 1.25/23.75- μ g of trimethoprim/sulfamethoxazole disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥ 16	Susceptible (S)
11-15	Intermediate (I)
≤ 10	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trimethoprim/sulfamethoxazole.

Quality Control

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 1.25/23.75- μ g trimethoprim/sulfamethoxazole disk* should provide the following zone diameters in these laboratory test quality control strains:

<u>Microorganism</u>		<u>Zone Diameter Ranges (mm)</u>
<i>Escherichia coli</i>	ATCC 25922	24–32
<i>Haemophilus influenzae</i> ^c	ATCC 49247	24-32
<i>Streptococcus pneumoniae</i> ^d	ATCC 49619	20-28

* Mueller-Hinton agar should be checked for excessive levels of thymidine or thymine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥ 20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

^c. This quality control range is applicable only to *Haemophilus influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)^{3,4}.

^d. This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood when incubated in 5% CO₂^{3,4}.

INDICATIONS AND USAGE

The components of this product, trimethoprim/sulfamethoxazole/phenazopyridine hydrochloride, are indicated in the treatment of urinary tract infections as follows:

Trimethoprim/Sulfamethoxazole is indicated for the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Morganella morganii*, *Proteus mirabilis* and *Proteus vulgaris*.

Phenazopyridine Hydrochloride is indicated for the symptomatic relief of pain, burning, urgency,

NDA 21-105
Page 8

frequency, and other discomforts arising from irritation of the lower urinary tract mucosa caused by infection. The use of phenazopyridine hydrochloride for relief of symptoms should not delay definitive diagnosis and treatment of causative conditions. Because it provides only symptomatic relief, prompt appropriate treatment of the cause of pain must be instituted and phenazopyridine hydrochloride should be discontinued when symptoms are controlled.

Phenazopyridine is compatible with antibacterial therapy and can help to relieve pain and discomfort during the interval before antibacterial therapy controls the infection. Treatment of a urinary tract infection with phenazopyridine hydrochloride should not exceed 2 days.
(See **DOSAGE AND ADMINISTRATION** section.)

CONTRAINDICATIONS

This therapy is contraindicated for use in patients with a known hypersensitivity to phenazopyridine hydrochloride, trimethoprim or sulfonamides and in those with renal insufficiency or documented megaloblastic anemia due to folate deficiency. Trimethoprim/sulfamethoxazole is also contraindicated in pregnant patients at term and in nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. Trimethoprim/sulfamethoxazole is contraindicated in pediatric patients less than two months of age.

WARNINGS

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, AND OTHER BLOOD DYSCRASIAS. SULFONAMIDES, INCLUDING SULFONAMIDE-CONTAINING PRODUCTS SUCH AS TRIMETHOPRIM/SULFAMETHOXAZOLE, SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious blood disorders (see PRECAUTIONS section).

Clinical signs, such as rash, sore throat, fever, arthralgia, pallor, purpura, or jaundice may be early indications of serious reactions.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

The sulfonamides should not be used for the treatment of group A beta-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including trimethoprim/sulfamethoxazole, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of

NDA 21-105

Page 9

clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *C. difficile*.

PRECAUTIONS

General

Trimethoprim/Sulfamethoxazole: Trimethoprim/sulfamethoxazole should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states), and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** sections).

Phenazopyridine Hydrochloride: A yellowish tinge of the skin or sclera may indicate accumulation due to impaired renal excretion and the need to discontinue therapy. The decline in renal function associated with advanced age should be kept in mind.

Geriatric Use

The use of trimethoprim/sulfamethoxazole by elderly patients may increase the risk of severe adverse reactions, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions or generalized bone marrow suppression (see **WARNINGS** and **ADVERSE REACTIONS** sections) or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function (see **DOSAGE AND ADMINISTRATION** section).

Information for Patients

Phenazopyridine Hydrochloride produces an orange to red color in the urine and may stain fabric. Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation. Staining of contact lenses has been reported.

This product contains two tablets: trimethoprim/sulfamethoxazole double strength is a white capsule-shaped scored tablet with beveled edges, plain on one side, scored in half on the other, with "93" embossed on one side of the breakline and "089" embossed on the other side and phenazopyridine hydrochloride is a round, sugar coated, deep maroon tablet imprinted "Z-U10" on one side. Trimethoprim/sulfamethoxazole double strength tablets should be taken every 12 hours for 10 days. Phenazopyridine Hydrochloride tablets should be taken 3 times a day after meals for no more than 2 days

NDA 21-105

Page 10

Laboratory Tests

Appropriate culture and susceptibility studies should be performed before and throughout treatment in patients receiving sulfamethoxazole/trimethoprim. Complete blood counts should be done frequently; if a significant reduction in the count of any formed blood element is noted, trimethoprim/sulfamethoxazole should be discontinued. Urinalysis with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Drug Interactions

In elderly patients concurrently receiving trimethoprim/sulfamethoxazole and certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. It has been reported that trimethoprim/sulfamethoxazole may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when trimethoprim/sulfamethoxazole is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Trimethoprim/sulfamethoxazole may inhibit the hepatic metabolism of phenytoin. Sulfamethoxazole/trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

Interaction between Trimethoprim/sulfamethoxazole and Phenazopyridine Hydrochloride

In a prospective two-way crossover drug interaction study between trimethoprim/ sulfamethoxazole double strength and phenazopyridine hydrochloride (200 mg) administered first singly, then in combination to 12 healthy female subjects for three days, it was determined that plasma concentrations of trimethoprim, sulfamethoxazole, and phenazopyridine hydrochloride were significantly increased compared to when either drug product was administered alone (see **CLINICAL PHARMACOLOGY** section). Some laboratory values were altered when phenazopyridine hydrochloride was administered concomitantly with trimethoprim/sulfamethoxazole. No values fell outside the normal range. The clinical significance of these changes is unknown.

**CHANGES* IN HEMATOLOGY AND CLINICAL CHEMISTRY PARAMETERS BETWEEN
SINGLE TREATMENT TRIMETHOPRIM/SULFAMETHOXAZOLE OR
PHENAZOPYRIDINE (TMP/SMX OR PZP)
AND
COMBINATION TREATMENT TMP/SMX AND PZP
(N=12)**

Parameter	Baseline [†] (SD)	PZP given alone [†] (SD)	TMP/SMX alone [†] (SD)	TMP/SMX and PZP in combination [†] (SD)	Normal Values
<i>HEMATOLOGY</i>					
Hemoglobin (gm/dL)	13.8 (1.0)	13.0 (0.8)	13.1 (0.9)	12.7 (0.9)	11.0-15.0
WBC (x10 ³ /μL)	7.0 (1.8)	8.1 (2.6)	7.7 (2.1)	7.2 (2.0)	4.0-10.0
<i>CLINICAL CHEMISTRY</i>					
Creatinine (mg/dL)	0.9 (0.2)	0.9 (0.1)	1.0 (0.1)	1.1 (0.2)	0.5-1.4
Total Bilirubin (mg/dL)	0.7 (0.2)	0.6 (0.2)	0.5 (0.1)	0.6 (0.2)	0.2-1.2
Direct Bilirubin (mg/dL)	0.3 (0.1)	0.1 (0.1)	0.3 [†] (0.0)	0.3 (0.2)	0.0-0.3
Indirect Bilirubin (mg/dL)	0.4 (0.2)	0.7 [†] (0.3)	0.17 (0.1)	0.8 (0.3)	0.0-1.1
SGOT (U/L)	24.2 (4.2)	25.3 (7.0)	24.8 (4.2)	27.2 (8.6)	14-36
SGPT (U/L)	31.3 (6.7)	31.3 (11.7)	32.8 (9.6)	34.1 (14.1)	11-56
Alkaline Phosphatase (U/L)	80.7 (19.1)	86.2 (15.4)	83.2 (15.9)	86.8 (16.4)	38-126

*Changes from baseline are statistically significant (p<0.05) unless otherwise noted

[†]Mean values

[†] Changes from baselines are *not* statistically significant

Drug/Laboratory Test Interactions

Due to its properties as an azo dye, phenazopyridine hydrochloride may interfere with urinalysis based on spectrometry or color reactions.

Sulfamethoxazole/Trimethoprim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimation of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sulfamethoxazole/Trimethoprim:

Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with sulfamethoxazole/trimethoprim.

Mutagenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay.

NDA 21-105

Page 12

In studies at two laboratories, no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels; at concentrations approximately 1000 times human plasma levels in these same cells, a low level of chromosomal damage was induced at one of the laboratories. No chromosomal abnormalities were observed in cultured human leukocytes at concentrations of trimethoprim up to 20 times human steady-state plasma levels. No chromosomal effects were detected in peripheral lymphocytes of human subjects receiving 320 mg of trimethoprim in combination with up to 1600 mg of sulfamethoxazole per day for as long as 112 weeks.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Phenazopyridine Hydrochloride:

Carcinogenesis: Long-term administration of phenazopyridine hydrochloride has induced neoplasia in rats (large intestine) and mice (liver). Although no association between phenazopyridine hydrochloride and human neoplasia has been reported, adequate epidemiological studies along these lines have not been conducted.

Mutagenesis: Adequate mutagenesis studies have not been performed with phenazopyridine hydrochloride.

Impairment of Fertility: There was no evidence of impaired fertility in rats administered doses of phenazopyridine hydrochloride up to 50 mg/kg/day.

Pregnancy: Teratogenic Effects. Pregnancy Category C

Trimethoprim/Sulfamethoxazole: In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead, resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

While there are no large, well-controlled studies on the use of trimethoprim and sulfamethoxazole in pregnant women, Brumfitt and Pursells⁵, in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or oral trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

NDA 21-105
Page 13

Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, trimethoprim/sulfamethoxazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Phenazopyridine Hydrochloride: Reproduction studies have been performed in rats at doses up to 50 mg/kg/day and have revealed no harm to the fetus due to phenazopyridine hydrochloride. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: See **CONTRAINDICATIONS** section.

Nursing Mothers

No information is available on the appearance of phenazopyridine hydrochloride or its metabolites in human milk. Trimethoprim/sulfamethoxazole is contraindicated in nursing mothers because sulfonamides are excreted in the milk and may cause kernicterus. (See **CONTRAINDICATIONS** section.)

Pediatric Use

This product is not recommended for pediatric patients (see **INDICATIONS AND USAGE** and **CONTRAINDICATIONS** sections).

ADVERSE REACTIONS

Trimethoprim/Sulfamethoxazole: The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria).

FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, OTHER BLOOD DYSCRASIAS AND HYPERSENSITIVITY OF THE RESPIRATORY TRACT (see **WARNINGS** section).

Phenazopyridine Hydrochloride: Headache, rash and occasional gastrointestinal disturbance. An anaphylactoid-like reaction has been described.

Methemoglobinemia, hemolytic anemia, renal and hepatic toxicity have been described, usually at overdosage levels (see **OVERDOSAGE** section).

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

Allergic: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schonlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa, and systemic lupus erythematosus have been reported.

NDA 21-105
Page 14

Gastrointestinal: Hepatitis, including cholestatic jaundice and hepatic necrosis, elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, and crystalluria.

Metabolic: Hyperkalemia, hyponatremia.

Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

Psychiatric: Hallucinations, depression, apathy, nervousness.

Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Musculoskeletal: Arthralgia and myalgia.

Respiratory System: Cough, shortness of breath, and pulmonary infiltrates (see **WARNINGS** section).

Miscellaneous: Weakness, fatigue, insomnia.

OVERDOSAGE

In case of an overdose of this product, patients should contact a physician, poison control center, or emergency room.

Trimethoprim/Sulfamethoxazole:

Acute: The amount of a single dose of trimethoprim/sulfamethoxazole that is either associated with symptoms of overdose or is likely to be life-threatening has not been reported. Signs and symptoms of overdose reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness, and unconsciousness. Pyrexia, hematuria, and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdose. Signs of acute overdose with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion, and bone marrow depression.

General principles of treatment include the institution of gastric lavage or emesis, forcing oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim.

The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

Chronic: Use of trimethoprim/sulfamethoxazole at high doses and/or for extended periods of time may

NDA 21-105
Page 15

cause bone marrow depression manifested as thrombocytopenia, leukopenia, and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin; 5 to 15 mg leucovorin daily has been recommended by some investigators.

Phenazopyridine Hydrochloride: Exceeding the recommended dose in patients with good renal function or administering the usual dose to patients with impaired renal function (common in elderly patients) may lead to increased serum concentrations and toxic reactions. Methemoglobinemia generally follows a massive, acute overdose. Methylene blue 1 to 2 mg/kg body weight intravenously or ascorbic acid 100 to 200 mg give orally should cause prompt reduction of the methemoglobinemia and disappearance of the cyanosis which is an aid in diagnosis. Oxidative Heinz body hemolytic anemia may also occur, and "bite cells" (degmacytes) may be present in a chronic overdosage situation. Red blood cell G-6-PD deficiency may predispose to hemolysis. Renal and hepatic impairment and occasional failure, usually due to hypersensitivity, may also occur.

DOSAGE AND ADMINISTRATION

Adults

Trimethoprim/Sulfamethoxazole: One (1) double strength (160 mg/ 800 mg) tablet every 12 hours for 10 days.

Phenazopyridine Hydrochloride: One (1) 200 mg tablet 3 times a day after meals. The administration of phenazopyridine hydrochloride should not exceed 2 days.

For Patients with Impaired Renal Function: When renal function is impaired, a reduced dosage of trimethoprim/sulfamethoxazole should be employed using the following table:

Creatinine Clearance (mL/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

HOW SUPPLIED

This product consists of a blister card containing trimethoprim/sulfamethoxazole double strength (160 mg/800 mg) tablets and phenazopyridine hydrochloride 200 mg tablets for oral administration as follows:

Twenty double strength (160 mg/800 mg) trimethoprim/sulfamethoxazole tablets, each a white capsule-shaped scored tablet with beveled edges, plain on one side, scored in half on the other, with "93" embossed on one side of the breakline and "089" embossed on the other side and six 200 mg phenazopyridine hydrochloride tablets, each a round, sugar coated, deep maroon tablet, imprinted "AP2" on one side.

NDC 53265-222-26

IN16027/01 05/01

NDA 21-105

Page 16

VC8130

Store at controlled room temperature 15°C-25°C (59°F-77°F) in a dry place and protected from light.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* – Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January, 2000.
2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing - Tenth Informational Supplement (Aerobic Dilution)*. NCCLS Document M100-S10 (M7), NCCLS, Wayne, PA, January, 2000.
3. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* – Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January, 2000.
4. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing - Tenth Informational Supplement (Disk Diffusion)*. NCCLS Document M100-S10 (M2), NCCLS, Wayne, PA, January, 2000.
5. Brumfitt W, Pursell R. Trimethoprim-sulfamethoxazole in the treatment of bacteriuria in women. *J Infect Dis.* November 1973;128 (suppl):S657-S663.

Phenazopyridine Hydrochloride 200 mg tablets are manufactured by:

Able Laboratories, Inc.

6 Hollywood Court,

South Plainfield, NJ 07080

Trimethoprim/sulfamethoxazole double strength tablets are manufactured by:

TEVA Pharmaceutical Industries, Ltd.

Kfar Sava Plant, 1 Hashikma Street

Industrial Zone

Kfar Sava, 44102 Israel

for Able Laboratories, Inc.

This product is packaged by:

Packaging Coordinators, Inc.

3001 Red Lion Road

Philadelphia, PA 19114

for Able Laboratories, Inc.